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Genetic deficiency of PRSS8 causes mouse intestinal inflammation and tumors

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PRSS8 is a glycosylphosphatidylinositol anchored serine protease, has physiological and pathophysiological functions and shows important roles in the epidermal barrier function and in the regulation of glucose homeostasis. However, the biological functions of PRSS8 in cancer initiation and progression is unknown. We have found that PRSS8 was significantly reduced in esophageal and colorectal cancers and acted as a tumor suppressor in colitis-associated colorectal cancer through targeting Sphk1/Stat3/Akt signaling pathway. To determine the roles of PRSS8 in colorectal cancer *in vivo*, we developed a conditional knockout mouse model - intestine-specific deletion of Prss8 in mice (Prss8 fl/fl-Cre+, Prss8 CKO), and found that PRSS8 deletion caused spontaneous formation of intestinal inflammation and tumors. At the age of 3 months, about 20% of the Prss8 CKO mice exhibited inflamed rectum and then exerted rectal prolapse. Histopathologic analysis showed that 65% Prss8 CKO mice had developed chronic inflammation in large intestine at 3 months. Interestingly, 45% Prss8 CKO mice had developed hyperplasia in small intestine at 3 months. At the age of 6 months, 53 % of the Prss8 CKO mice developed adenomas, and at the age of 9 months, 75% of the Prss8 CKO mice developed adenomas. Further studies showed that gastrointestinal tumorigenesis was linked to the disruption of intestinal epithelial cell maturation: more proliferative cells and moved faster in the Prss 8 CKO mouse, assayed by BrdU staining and migration assay. Moreover, Prss 8 CKO mouse intestine exhibited less mature mucin drops and goblet cells at the crypts of small and large intestine in comparison with the WT mice. Gene profile using mouse intestinal epithelial cells and gene set enrichment analysis showed that the tumorigenesis was associated with oncogenic signaling pathways, including Wnt/beta-catenin and inflammatory signaling. The underlying mechanisms are under further investigation.

Biography

Yonghua Bao graduated from Jiamusi Medical University (China) with a Clinical Medicine background, received PhD on Biochemistry and Molecular Biology from Jilin University and Post-doctoral training on Biochemistry and Molecular Biology in the State Key Laboratory of China Agricultural University. She was promoted as Associate Professor and worked in cancer and cell signal transduction lab since 2012. She was recruited by Jining Medical University as a Professor of Pathology in 2015, and was appointed as Vice Dean of Institute of Precision Medicine. Her study focuses on cancer biology and cell signaling pathways in gastrointestinal carcinogenesis, progression and metastasis. As PI, she was funded by the National Natural Science Foundation of China. She has published 22 papers and was awarded 3 patents.

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